REMARKS

Applicants file this response in conjunction with a Request for Continued Examination (RCE). Claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42, 43, and 57-60 are pending in this application. Claims 4-6, 8-10, 15-19, 23-31, 36, 37, 39-41, and 44-56 have been cancelled.

In this response, applicants have amended claims 1, 7, 32, and 38 and added new claims 59 and 60. These amendments and new claims add no new matter. In particular, the new language added to these claims is supported in the application as published, e.g., in the Abstract, at paragraphs 0040, 0050, 0060, 0063, and in Examples 4, 6, 7, 8, and 9, which all show the use of vaccines that protect various mammals against subsequent, otherwise lethal, challenges with the H1N1 influenza virus.

Applicants respectfully submit that the prior art does not disclose or suggest the presently claimed invention, which includes methods of immunizing a vertebrate against an H1N1 influenza virus infection, and that the Examiner should not mistake mere prophetic examples and speculation in the presently cited prior art, such as Felgner et al., PCT WO90/11092, as facts to support an alleged obviousness rejection.

Withdrawn Rejections

Applicants note with appreciation that the Office has withdrawn the rejections under nonstatutory obviousness-type double patenting.

35 U.S.C. § 103

The Office rejected claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42, 43, 57, and 58 as allegedly obvious over Felgner et al. (WO90/11092; "Felgner") in view of Huylebroeck et al. (Gene, June 1988, 66(2): 163-81; "Huylebroeck"), Townsend et al. (Cell, November 1984, 39(1): 13-25), Atkinson et al. (U.S. Pat. No. 4,861,864; "Atkinson"), and Andrianov et al. (U.S. Pat. No.5,529,777; "Andrianov"). Applicants traverse this rejection for the following reasons.

The present claims are directed to a method of immunizing a vertebrate against an H1N1 influenza virus infection. The method includes administering to a vertebrate, prior to infection

by an H1N1 influenza virus, a composition consisting essentially of a plurality of the same plasmid vectors in a physiologically acceptable medium, the plasmid vectors comprising DNA encoding an H1N1 influenza virus antigen operatively linked to DNA which is a promoter, whereby a protective immune response comprising both a humoral immune response and a cell-mediated immune response is elicited against the antigen, to thereby protect the vertebrate against disease caused by a subsequent infection by an H1N1 influenza virus.

The Office alleged (at page 7 of the Office Action) that "... the scope of the claims provides only general parameters for providing a 'protective immune response' and Felgner does teach or suggest a 'protective immune response,'..." Applicants respectfully disagree. The recited method requires administration of a DNA vaccine to a vertebrate, prior to infection by an H1N1 influenza virus, to illicit a protective immune response to protect the vertebrate against a subsequent infection by the H1N1 influenza virus. This type of *prophylactic* response is very different from a *therapeutic* treatment of an existing viral infection. This concept is clear from the specification and is exemplified in the examples, in which BALB/C mice and ferrets were used in the tests. While Felgner generally discloses the introduction of DNA or RNA into vertebrates for a variety of applications, including so-called immunization, applicants have found no actual data in Felgner to suggest that DNA vaccines can be used to successfully immunize a subject against subsequent infection from an H1N1 influenza virus, or any virus for that matter.

The Office Action states (at page 6):

> Example 8 of Felgner et al. teach a mRNA vaccination of mice with gp120 protein of HIV virus (pages 55-56) and subsequent analysis of antibodies produced in the mouse with are immunogenic against gp120. In an art recognized in *vitro* assay system having CD4+ cells, Felgner et al demonstrated that mouse serum containing anti-gpl20 antibodies from the vaccinated mice is able to lyse the CD4+ cells (page 56) ... In this experiment, Felgner demonstrates a humoral immunity protective effect against the HIV infection of cells.

Applicants note that the portion in Example 8 (at page 56, lines 3-22) cited by the Office regarding the in *vitro* assay having CD4+ cells is written in the present tense, meaning that this portion is merely prophetic. Felgner merely states, without disclosing any actual supporting data, that "[the] protective effect of gp120 immune serum is determined as the reduction in the number of plaques in the batches of cells treated with both gp120 mRNA-vaccinated mouse serum and HIV compared to the number in batches treated with HIV alone (*emphasis added*)."

Thus, Felgner does not disclose any actual data that demonstrates that serum containing anti-gpl20 antibodies from vaccinated mice is able to lyse the CD4+ cells.

The Office further asserted (at page 9 of the Office Action):

> Example 9 of Felgner shows in a nude mouse with a reconstituted human immune system, nucleic acid vaccination of these mice showed an anti-viral protection after subsequent infection of the mouse with a virus (page 57, lines 24-25). To the examiner, the Felgner reference seems to indicate that there is some predictability in producing protective immune response in a subject from a subsequent viral infection.

Applicants disagree. Example 9 describes (at page 56, line 25, to page 57, line 25) actual data regarding injecting already HIV-infected mice with a liposome formulation containing RNA encoding the HIV *nef* protein, and assaying the anti-viral effect of blood samples obtained from the treated mice in an *in vitro* plaque assay. Referring to the results of the plaque assay, Felgner states (at page 57, lines 24-25) that "... these results indicate a moderate anti-viral effect of the (*in vivo*) treatment (*emphasis added*)." Example 9 then goes to state (at page 57, lines 26-35):

> A volume of 200 µl of the formulation, containing 200 µg/ml of *nef* mRNA, and 500 µg/ml 1:1 DOTAP:DOPE in 10% sucrose is injected into the tail vein of the human stem cell-containing SCID mice 3 times in one day. Following immunization, the mice are challenged by infection with an effective dose of HIV virus. Samples of blood are periodically withdrawn from the tail vein and monitored for production of the characteristic HIV protein p24 by an ELISA kit assay (Abbott Labs, chicago, IL) (*emphasis added*).

Thus, this portion of Example 9 is written in the present tense, and is merely prophetic. There is no actual data demonstrating that *nef* RNA induces a protective immune response in SCID mice against a subsequent HIV infection. Thus, Felgner describes data regarding treatment of an existing HIV infection, but no data whatsoever to show that the treatment can work to vaccinate a subject prior to infection, to provide protective immunity against disease caused by a later infection.

In summary, the Office has not pointed to any actual evidence to show that skilled practitioners would have expected a prophylactic DNA vaccine to be successful based on the disclosure of Felgner. In any event, whatever data Felgner discloses regarding immunization are limited to HIV. Thus, not only does Felgner fail to disclose a DNA vaccine against an H1N1 influenza virus, reading the reference, skilled practitioners also would not have expected a DNA vaccine to successfully immunize a subject against H1N1 viral infection.

Huylebroeck does not remedy the deficiencies of Felgner. This reference discloses plasmid vectors for transient expression of DNA in animal cells (see, e.g., Abstract), and the use of these vectors to express H3N2 influenza hemagglutinin HA and H1N1 influenza matrix protein M_1 in cultured cells (see, e.g., at page 173, right column). According to Huylebroeck (at page 179, right column, second paragraph), these vectors are useful tools because "... [transient] expression is a valuable and rapid system for investigating polypeptide regions responsible for various properties of viral antigens, in particular the immunogenicity, receptor-binding, enzymatic or fusogenic activities of membrane-bound glycoproteins ... (emphasis added)." There is nothing here that would have lead skilled practitioners to use these vectors to immunize vertebrates against later influenza infections.

This concept of using expression vectors as tools to study polypeptides expressed *in vitro* differs markedly from the concept of administering DNA directly to a subject for expression *in vivo* for immunizing the subject. Huylebroeck does not even suggest the concept of DNA vaccines, and thus provides no further information regarding DNA vaccination to supplement the disclosure of Felgner. Accordingly, even assuming that skilled practitioners would have combined the teachings of Felgner and Huylebroeck, they would not have had an expectation that a vector encoding a viral antigen could be used successfully as a vaccine that protects against a subsequent challenge. Thus, the instant claims would not have been obvious over Felgner and Huylebroeck, individually or combined.

The Office also cites Townsend, but this reference similarly fails to rectify the deficiencies of Felgner and Huylebroeck. Townsend (at page 13, right column, the first full paragraph) used established cell lines expressing individual influenza genes "... to compare the roles played by the nucleoprotein and hemagglutinin molecules in target cell recognition by influenza A specific cytotoxic T cells." Like Huylebroeck, using transfected cells to study viral proteins *in vitro* does not provide any suggestion for a DNA vaccine that provides a protective immune response. The Office (at page 10) cites Townsend for disclosing plasmids encoding hemagglutinins and routine isolation of influenza genes. However, the mere ability to construct a plasmid expressing an influenza gene is not the same as the ability to use the plasmid as an effective DNA vaccine against subsequent influenza infections.

The Office (at page 11) further points to Townsend for suggesting a vaccine that presents nucleoprotein in an appropriate form. While Townsend does make such a suggestion, it does so in the context of a discussion of whether cytotoxic T cells can also recognize denatured peptides presented on the cell surface, and not only viral antigens in their native conformation (see page 22, right column, the first two paragraphs). Applicants fail to see how this disclosure would have led skilled practitioners to any DNA vaccine, much less the expectation that a DNA vaccine would successfully immunize a vertebrate. In view of the foregoing, Townsend would not have led skilled practitioners to a method for immunizing a subject by direct administration of DNA to the subject. Furthermore, like Felgner and Huylebroeck, Townsend also fails to provide a reason for skilled practitioners to reasonably expect that such a method would have been successful. Accordingly, these three references, individually or combined, do not render the instant claims obvious.

Since the present claims do not recite rotavirus and polymer encapsulated antigen, Atkinson and Andrianov are no longer relevant to the present rejection, as the Office acknowledged (at page 8 of the Office Action).

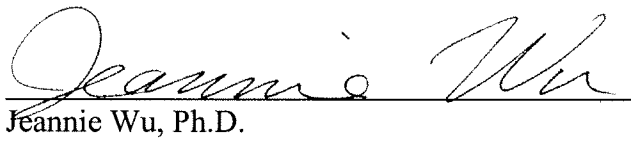
In view of the above, even assuming that skilled practitioners would have been led to combine the teachings of all of the cited references, they would not have had any expectation, much less a reasonable expectation, that direct administration of DNA encoding an H1N1 influenza viral antigen to a subject, prior to an infection of that subject by the H1N1 influenza virus, could successfully immunize the subject against a disease caused by a subsequent viral infection. Thus, the instant claims would not have been obvious. Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The extension fee and the RCE fee are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket 07917-0217002.

Respectfully submitted,

Date: November 12, 2009



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